Radical Reactions

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Redox-Active Reagents for Photocatalytic Generation of the OCF_3 Radical and (Hetero)Aryl C–H Trifluoromethoxylation

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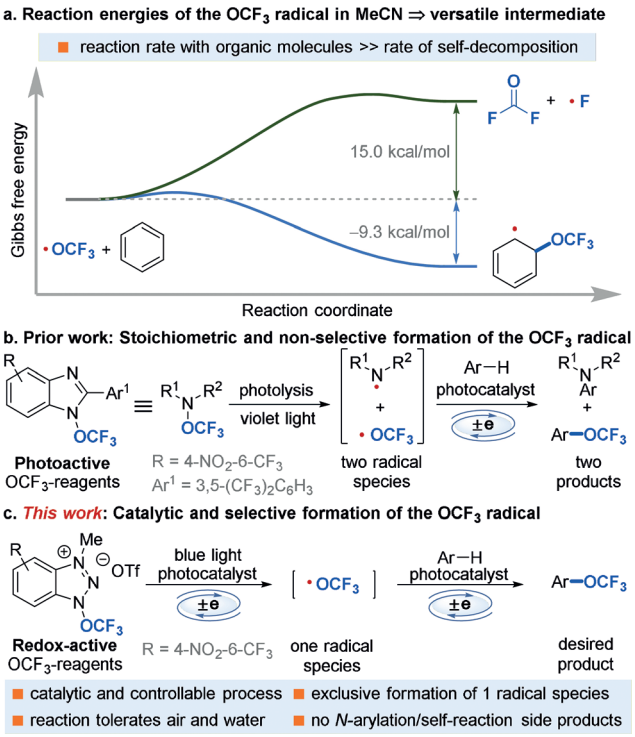
Abstract: *The trifluoromethoxy (OCF_3) radical is of great importance in organic chemistry. Yet, the catalytic and selective generation of this radical at room temperature and pressure remains a longstanding challenge. Herein, the design and development of a redox-active cationic reagent (**1**) that enables the formation of the OCF_3 radical in a controllable, selective, and catalytic fashion under visible-light photocatalytic conditions is reported. More importantly, the reagent allows catalytic, intermolecular C–H trifluoromethoxylation of a broad array of (hetero)arenes and biorelevant compounds. Experimental and computational studies suggest single electron transfer (SET) from excited photoredox catalysts to **1** resulting in exclusive liberation of the OCF_3 radical. Addition of this radical to (hetero)arenes gives trifluoromethoxylated cyclohexadienyl radicals that are oxidized and deprotonated to afford the products of trifluoromethoxylation.*

The OCF_3 radical is of significant interest to synthetic chemists because this open-shell intermediate has reactivity that is complementary with and difficult to achieve by the OCF_3 anion.[1] While the weakly nucleophilic CF_3O anion often requires activated electrophiles such as carbocations,[2] the reaction rate of the reactive OCF_3 radical with unactivated organic compounds (e.g., benzene) is more favourable than that of self-decomposition (Scheme 1 a). Thus, easy-to-handle reagents capable of liberating the versatile OCF_3 radical at room temperature are highly desired because it not only creates a reaction platform for the design and development of novel trifluoromethoxylation reactions of hydrocarbons but also provides direct access to the underexplored OCF_3 chemical space.[3]

Seeking to develop OCF_3-radical reagents for trifluoromethoxylation of hydrocarbons, we took advantage of the weak N–OCF_3 bond (BDE = 53.1 kcal mol^{-1}) and recently reported a photoactive OCF_3-reagent that could be photolyzed under irradiation with violet light (λ_{max} = 402 nm) to form the OCF_3 radical and an *N*-centered benzimidazole radical (Scheme 1 b).[3m] Although the reagent is capable of trifluoromethoxylation of arenes, the reaction is complicated by the formation of the *N*-arylated side products (3–10%). Additionally, the formation of the OCF_3 radical is a stochiometric process because whenever the reagent is photoexcited, the N–OCF_3 bond would homolyze to form two radical species. We questioned whether the OCF_3 radical could be generated catalytically and selectively using a redox-active OCF_3-reagent. Herein, we report the design and development of such a reagent bearing a benzotriazole core for a direct, catalytic C–H trifluoromethoxylation of (hetero)arenes (Scheme 1 c).



Scheme 1. Formation and reactions of the OCF_3 radical.

Our redox-active reagents are based on 1-hydroxy-benzotriazole scaffolds because these compounds, widely used in peptide synthesis, are inexpensive. Additionally, they can be easily prepared through a one-step condensation reaction of *ortho*-halonitrobenzene with hydrazine, which allows rapid exploration of the structure–reactivity relationship of OCF_3-reagents.[4] Moreover, we have successfully established a reaction protocol for the synthesis of 1-OCF_3-benzotriazole compounds (e.g., **A**, Table 1). More importantly, *O*-acylated 1-hydroxy-benzotriazoles are capable of accepting an electron to form the corresponding radical anion leading to the mesolytic cleavage of the N–O to afford an *O*-centered

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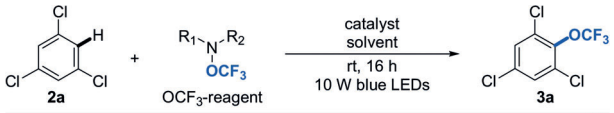
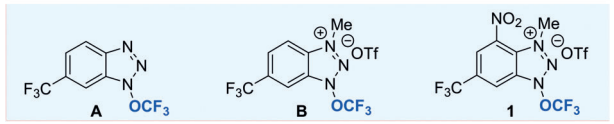
Table 1: Selected optimization experiments.[a]



Entry	Reagent (1 equiv)	Catalyst (1 mol%)	Solvent (0.200 M)	Yield[b] 3a
1	**A**	$Ru(bpy)_3(PF_6)_2$	CH_3CN	0%
2	**B**	$Ru(bpy)_3(PF_6)_2$	CH_3CN	60%
3	**1**	$Ru(bpy)_3(PF_6)_2$	CH_3CN	70%
4	**1**	**$Ru(bpy)_3(PF_6)_2$**	**$MeCN/CH_2Cl_2$ (1:1)**	**84%**
5[c]	**1**	$Ru(bpy)_3(PF_6)_2$	$MeCN/CH_2Cl_2$ (1:1)	51%
6	**1**	-	$MeCN/CH_2Cl_2$ (1:1)	<5%
7[d]	**1**	$Ru(bpy)_3(PF_6)_2$	$MeCN/CH_2Cl_2$ (1:1)	<5%
8[e]	**1**	$Ru(bpy)_3(PF_6)_2$	$MeCN/CH_2Cl_2$ (1:1)	82%
9[f]	**1**	$Ru(bpy)_3(PF_6)_2$	$MeCN/CH_2Cl_2$ (1:1)	80%



[a] 10 equivalents of **2a** was used. [b] Yields were determined by ^{19}F-NMR using $PhCF_3$ as an internal standard. [c] 1 equivalent of **2a** was used. [d] Without light. [e] Under air atmosphere. [f] With 100 equivalents of H_2O.

radical.[5] Thus, a series of 1-OCF_3-benzotriazole reagents were synthesized.

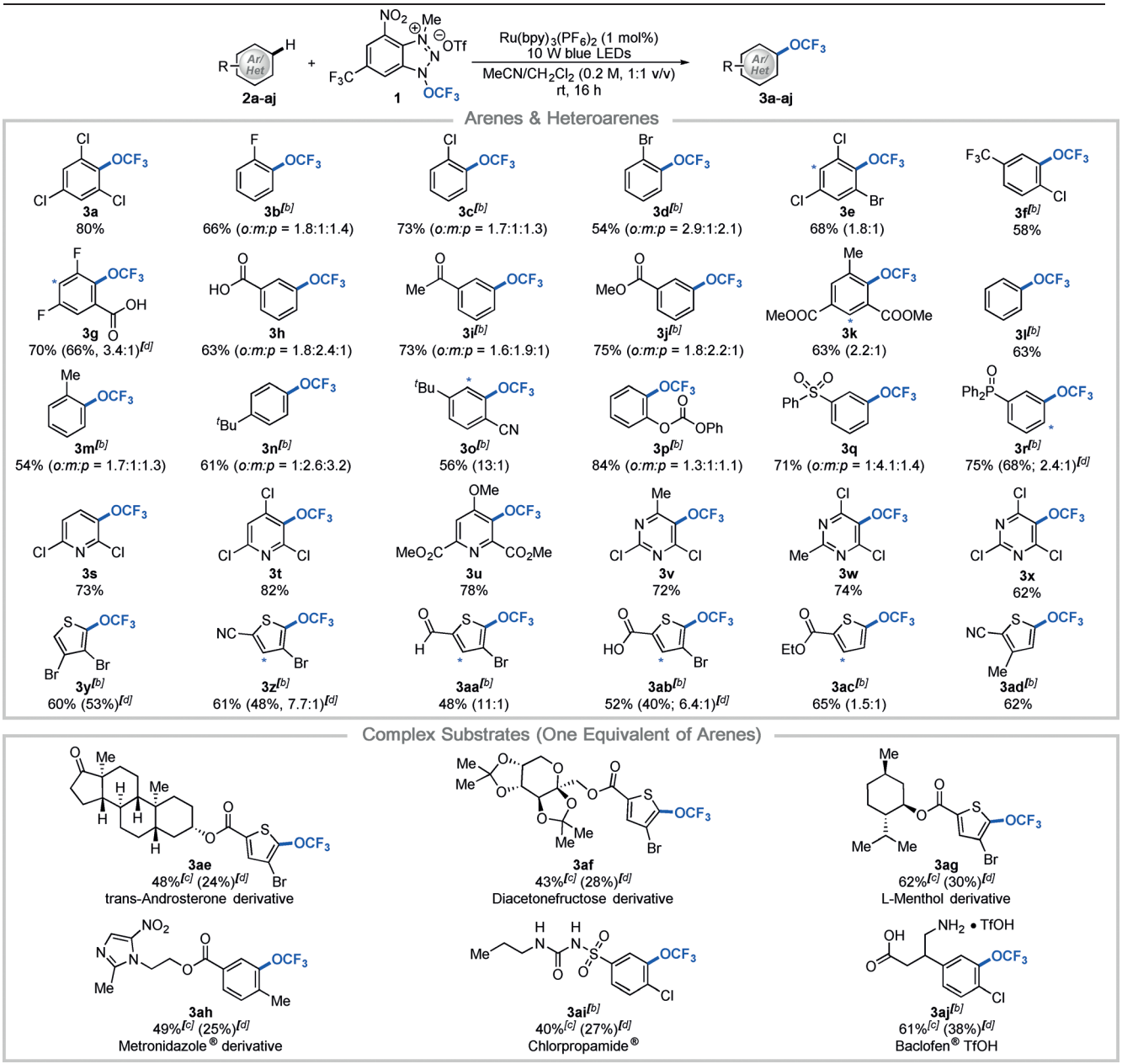
Photoredox catalysis has recently emerged as a powerful tool in organic synthesis.[6] We hypothesised that an appropriate combination of photoredox catalysts and 1-OCF_3-benzotriazole reagents would allow the catalytic formation of the OCF_3 radical through a sequential SET process. An initial attempt to subject compound **A** (1 equiv) to a mixture of 1,3,5-trichlorobenzene (**2a**, 10 equiv) and $Ru(bpy)_3(PF_6)_2$ (1 mol%) in MeCN (0.200 M) under irradiation with 10 W blue LED light ($\lambda_{max} = 447$ nm) failed to produce the desired product **3a** (Table 1, entry 1). Presumably, this is due to the highly negative reduction potential of **A** ($E_p = -1.97$ V vs. saturated calomel electrode (SCE); Supporting Information, Figure S12). Even if the corresponding radical anion can be accessed, DFT calculations show that the mesolytic cleavage of the N–OCF_3 bond would favour the formation of the *N*-centered benzotriazole radical rather than that of the OCF_3 radical because of the electron withdrawing group (e.g., CF_3) on the O atom (Figure S6).[3m,7] We reasoned that cationic N–OCF_3 reagents would be better electron acceptors and the resulting reduced neutral radicals would fragment to form the OCF_3 radical selectively (Scheme 2a, see below). Indeed, using methylated cationic reagent **B** instead of **A** under otherwise identical conditions gave **3a** in 60% yield along with 33% of byproducts **B′** (entry 2).[8] Deactivation of the benzotriazole ring with an addition of a nitro-group (reagent **1**) suppressed the formation of **B′** and increased the product yield to 70% (entry 3). Using a solvent mixture of MeCN and CH_2Cl_2 (1:1 v/v) further improved the yield to 84% (entry 4) and no *N*-arylated side product was observed. The reaction also worked with one equivalent of trichlorobenzene albeit in a lower yield and accompanied by 15% of bis-trifluoromethoxylated product (entry 5). Control experiments confirmed the necessity of the visible light and photoredox catalysts (entries 6 and 7). Notably, the reaction proceeded under an air atmosphere or in the presence of water without loss of reactivity (entries 8 and 9).

With the optimized conditions (Table 1, entry 4) in hand, we turned our attention to explore the generality of the transformation. To our delight, a wide range of mono-, di-, and tri-substituted (hetero)arenes reacted well to afford the desired C–H trifluoromethoxylation products (Table 2). Functional groups such as halides (F, Cl, Br, **2a–2g**, **2s–2t**, **2v–2ab**, **2ae–2ag**, and **2ai–2aj**), carboxylic acids (**2g–2h**, **2ab,** and **2aj**), ketones (**2i** and **2ae**), esters (**2j–2k**, **2u**, **2ac**, **2ae–2ah**), aldehyde (**2aa**), urea (**2ai**), substrates with weak benzylic hydrogen atoms (BDE ≈ 88 kcal mol^{-1}, **2m**, **2v–2w**, **2ad**, **2ah**,and **2aa**),[9] nitrile (**2o**, **2z**, and **2ad**), nitro (**2ah**), sulfonyl (**2q** and **2ai**), phosphine oxide (**2r**), and CF_3 (**2f**) groups are all tolerated. In contrast to the previously reported photoactive reagent,[3m] redox-active reagent **1** could be used to functionalize electron-rich arenes such as toluene (**2m**) and *tert*-butyl benzene (**2n**), affording the desired products in synthetically useful yields. Notably, heteroarenes such as pyridine, pyrimidine, and thiophene (**2s–2ad**), found in thousands of medicinally important structures, could also be used in this reaction. Although ten equivalents of arenes were used, we could recover 7.9–9.2 equivalents of aromatic substrates at the end of the reaction, which is critical for valuable arenes. The synthetic utility of this process is further highlighted by its amenability to a late-stage trifluoromethoxylation of biorelevant molecules using arenes as a limiting reactant. For example, *trans*-androsterone, diacetonefructose, L-menthol (analgesics and decongestants), and Metronidazole (antibiotic) derivatives reacted to afford the desired OCF_3-analogs (**3ae–3ah**) in modest yields based on the recovery of starting materials. Other marketed drugs such as Chlorpropamide (anti-diabetic drug, **2ai**) and Baclofen (muscle relaxant, **2aj**) were viable substrates as well.

The regioselectivity of the reaction resembles other radical-mediated aromatic substitution processes and is guided by the electronics of the substituent except in the case of a bulky substituent, for example, substrate **2o**, for which the OCF_3 radical adds preferably to the position distal from the *tert*-Bu group. Additionally, if an aromatic substrate has multiple reaction sites, the OCF_3 radical will add to these sites to form regioisomers. Isolation of these regioisomers allows rapid biological-activity assays of OCF_3-analogs and accelerates the discovery of new drugs.[10]

Our unique ability to catalytically and selectively generate the OCF_3 radical at ambient conditions allows studying its property and reactivity in organic solvents. Intermolecular competition experiments demonstrated that the electrophilic OCF_3 radical reacts favourably with an electron-rich arene (Supporting Information, Figure S8). Deuterium kinetic isotope effect (KIE) studies showed no KIE (Figure S9), which rules out the possibility of H-atom abstraction/deprotonation as the rate-determining step. Determination of the quantum yield and quenching constant through Stern–Volmer quenching studies proved to be challenging because the $Ru(bpy)_3^{2+}$ sensitiser and reagent **1** both absorb in the visible light region (Figures S3 and S4). Nevertheless, light on/off experiments

Table 2: Selected examples of (hetero)aryl C–H trifluoromethoxylation.[a]



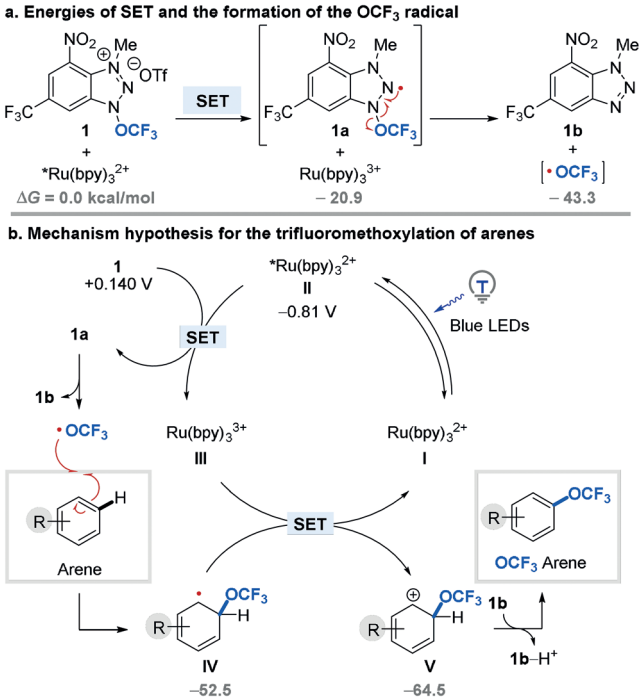
[a] Reactions were performed using 1 equivalent of **1** and 10 equivalents of (hetero)arenes. Yields and regioselectivity were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [b] MeCN was used as the solvent. [c] Reactions were performed using 1 equivalent of substrates and 2 equivalents of reagent **1**. The isolated yield based on the recovered starting material. [d] Yield in parenthesis is the isolated yield.

showed that the reaction halted when the irradiation stopped (Figure S10), which indicates that an extended radical chain mechanism is unlikely. This corroborates with DFT calculations, in which SET between $Ru(bpy)_3^{3+}$ and **IV** is more favourable than the chain mechanism (Figure S7). Since the reaction is insensitive to oxygen (Table 1, entry 8), reagent **1** should quench excited $Ru(bpy)_3^{2+}$ faster than molecular oxygen and have the quenching constant of at least $2.7\times10^9\,M^{-1}s^{-1}$.[11] Finally, DFT calculations showed favourable SET between excited $*Ru(bpy)_3^{2+}$ and **1** to form neutral radical **1a** ($\Delta G = -20.9$ kcal mol^{-1}) that readily undergoes homolytic cleavage of the N–OCF_3 bond ($\Delta G = -22.4$ kcal mol^{-1}), thereby catalytically and exclusively delivering the OCF_3 radical (Scheme 2a).

Based on the collective results, a catalytic cycle proposed in Scheme 2b serves as a working mechanistic hypothesis. Initial excitation of the $Ru(bpy)_3^{2+}$ (**I**, bpy = 2,2′-bipyridine) produces the long-lived triplet-excited state of $*Ru(bpy)_3^{2+}$ (**II**, $t_{1/2} = 1.1$ μs).[12] Catalyst **II** is sufficiently reducing ($E_{1/2}^{red} = -0.81$ V) to undergo SET with the redox-active reagent **1** ($E_p = +0.140$ V, vs. SCE in CH_3CN, Figure S10) to generate $Ru(bpy)_3^{3+}$ and neutral radical **1a** that fragments to exclusively liberate the OCF_3 radical. Its addition to an arene to form cyclohexadienyl radical **IV** is thermodynamically

favourable ($\Delta G = -9.2$ kcal mol^{-1}). Oxidation of **IV** by Ru(bpy)$_3^{3+}$ affords cyclohexadienyl cation **V**, which is deprotonated to give the desired product of trifluoromethoxylation.

In conclusion, we describe the air- and moisture-stable, redox-active reagent **1** that enables catalytic and selective generation of the OCF_3 radical under visible-light photocatalytic conditions at room temperature. A key design feature of the reagent is its cationic nature that favours the formation of a single OCF_3 radical species after the SET reduction. Reagent **1** is applicable to the synthesis of an important class of OCF_3-arenes and late-stage C–H trifluoromethoxylation of biorelevant molecules. Mechanistic studies suggest a catalytic cycle distinct from the previously reported photoactive OCF_3-reagent. Upon completion of this work, Togni et al. reported an elegant radical trifluoromethoxylation reaction using a similar concept.[13] Their protocol uses cationic pyridinium OCF_3 reagents, first developed by Umemoto and Hu,[14] to generate the OCF_3 radical under photocatalytic conditions. We anticipate that the unique ability to catalytically access the OCF_3 radical using their and our reagents will open a new avenue for the development of trifluoromethoxylation reactions to aid the discovery of novel functional molecules.



Scheme 2. Reaction energies and the proposed catalytic cycle. DFT calculations were performed at the M06-2X/6-311++G(d,p)/SMD-(MeCN)//M06-2X/6-31+G(d) level of theory using benzene as the substrate. All energies are in kcal mol^{-1} and are with respect to **II** and **1**. See the Supporting Information for details.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arenes · photocatalysis · radicals · trifluoromethoxylating reagents · trifluoromethoxylation

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Communications

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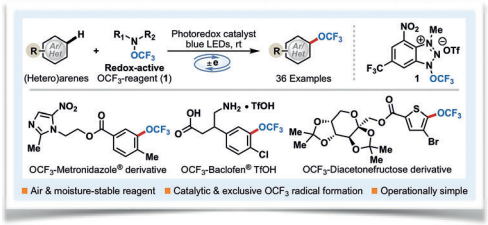

One Radical at a Time: Redox-active cationic OCF_3 reagents enable catalytic and selective formation of the OCF_3 radical under visible-light photocatalytic conditions. Its synthetic utility is highlighted by late-stage C–H trifluoromethoxylation of (hetero)arenes and biorelevant molecules.

